



Armed Forces College of Medicine

AFCM

09/20/2024

Genitourinary module

Medical

Microbiology and Immunology



Viral genital tract infections

Dr. Alaa Ahmed Aly

Professor of Medical Microbiology & Immunology

09/20/2024

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INTENDED LEARNING OBJECTIVES (ILO)



By the end of this session the student will be able to:

- 1-Describe pathogenesis & clinical manifestations of Viral genital tract infections
- 2-Outline laboratory diagnosis of Viral genital tract infections
- 3-Outline prevention of Viral genital tract infections



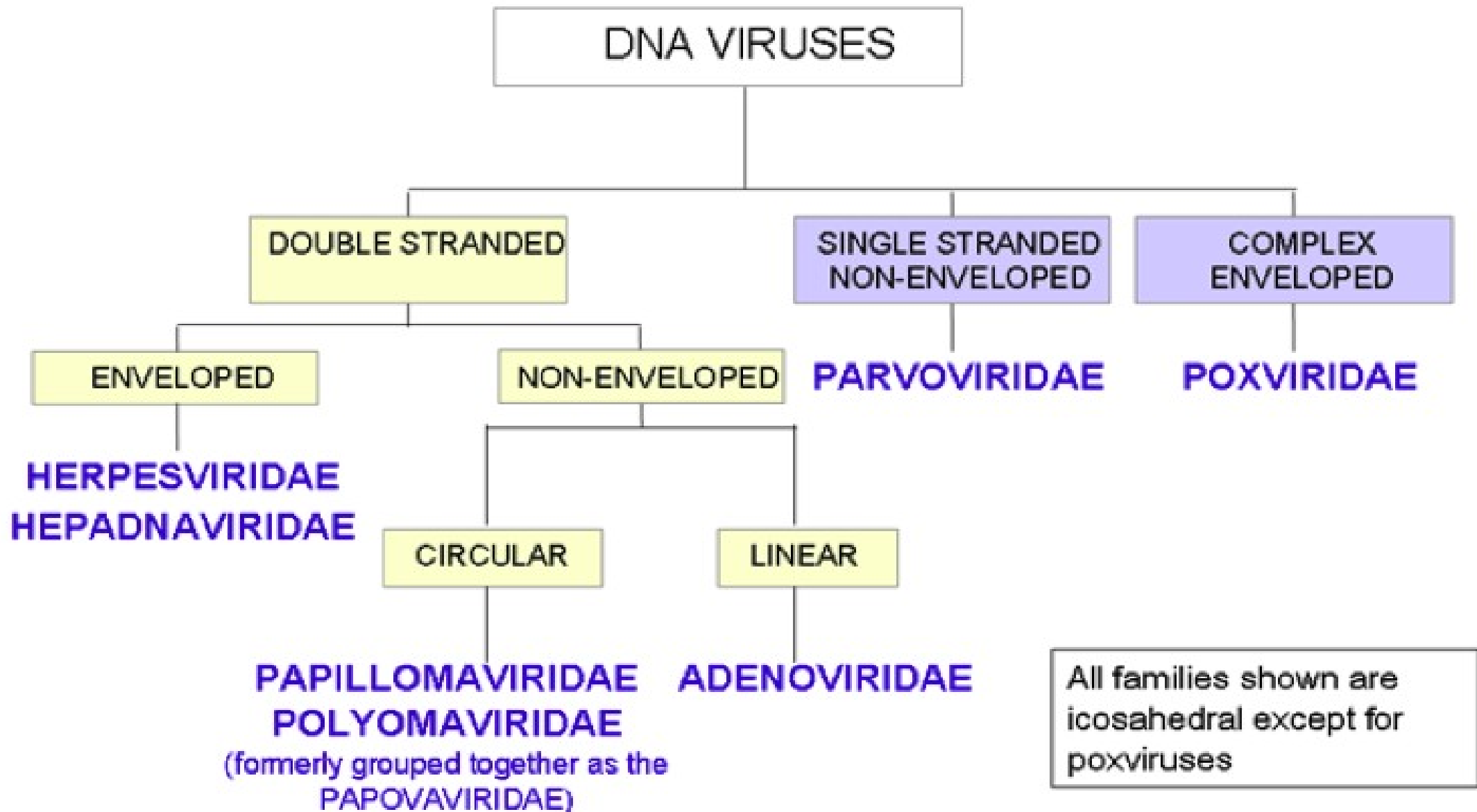
Genital Warts

Human papilloma virus

Molluscum contagiousum virus



**Generally benign
growths
of the epithelium
of the skin & mucosa**



Human papilloma virus (HPV)



Structure

A - Nucleocapsid

1- Genome : dsDNA divided into 2 main regions

a -Early region : with multiple genes (E1-E7)

Encode proteins responsible for **pathogenecity**

b-Late region with 2 genes (L1&L2)

Encode **capsid proteins**

2- Icosahedral

B - Non Enveloped

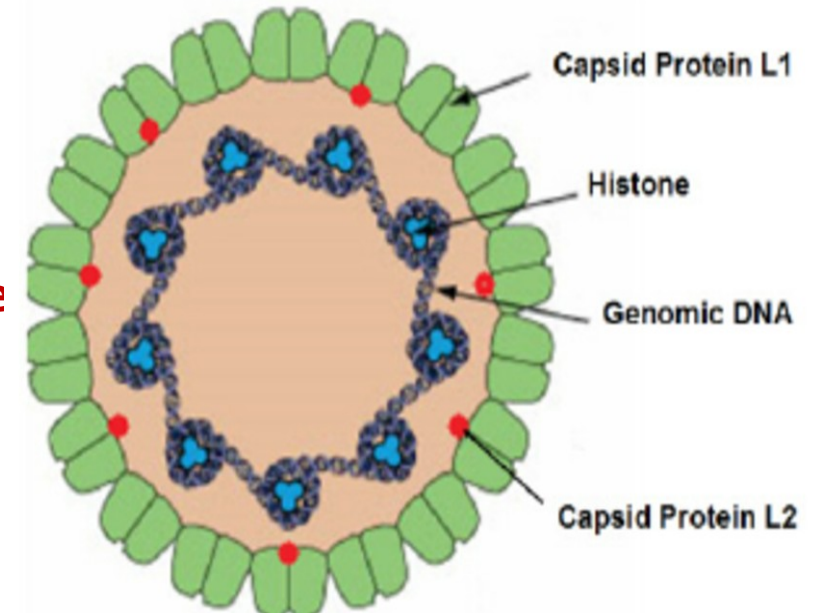
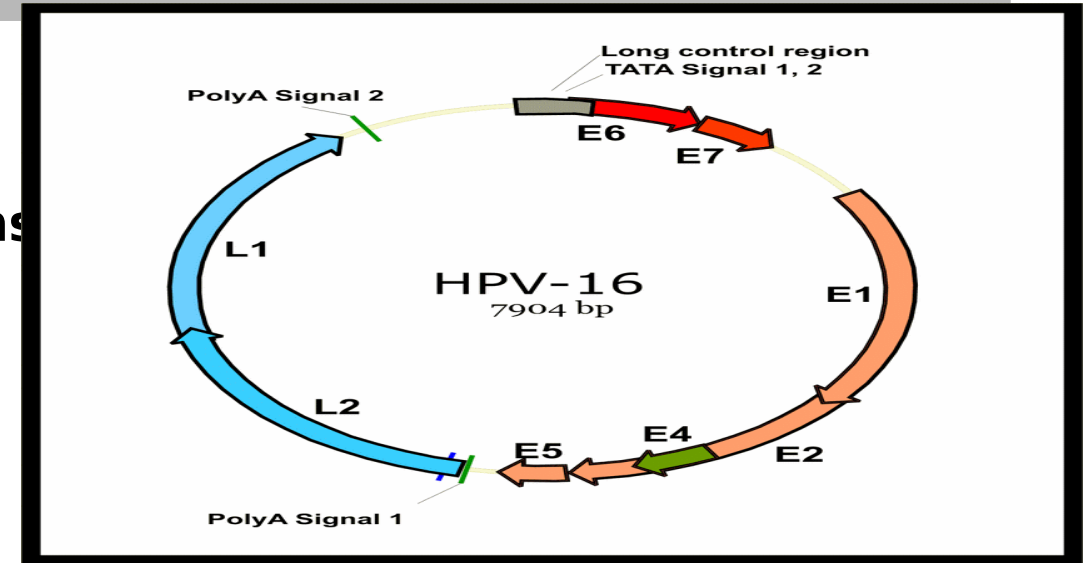
C-Classification

>100 types according to DNA differences (L1 nucleotide sequence)

→ Further grouping according to :

1 Site of infection : Cutaneous , mucosal or genital HPVs

2-Potential association with cancer : Low or high (14 types) :



Human papilloma virus (HPV)



Pathogenesis

A- Mode of transmission

1-Skin-to-skin contact (commonest route)

2-Indirect contact through fomites (e.g damp surfaces & towels)

***Virus is stable (non-enveloped)**



Spread indirectly from contaminated floor, edge of swimming pool, etc.

(Wet skin is more vulnerable to surface breaks)

3- Sexual contact.

4-From an infected mother to the neonate during childbirth



HPV Transmission

- **Sexual**
 - Intercourse
 - Genital (non-penetrative), oral, digital contact (skin to skin contact)
 - Condoms help, but not completely protective
- **Non-sexual**
 - Mother to newborn (vertical transmission - rare)
 - Possibly via fomites ^{1,2} (underwear, equipment)
 - Can be seen in virgins (rare)

¹ Roden, RB et. al, J Infect Dis. 1997 Oct;176(4):1076-9; ² Ferenczy A, et. al, Obstet Gynecol. 1989 Dec;74(6):950-4

Human papilloma virus (HPV)



B-Effects

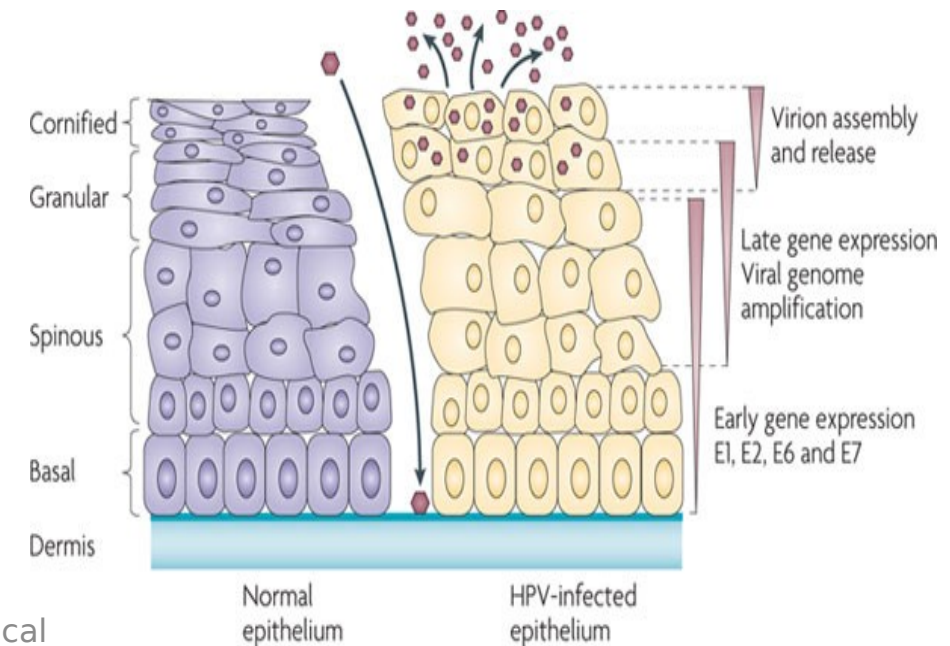
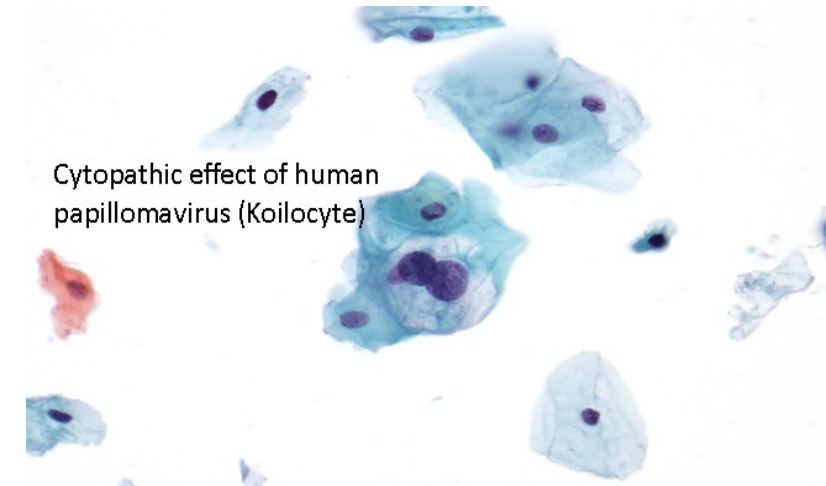
1-HPVs cause warts (papillomas)

a-Induce epithelial cell proliferation with

formation of koilocytes :infected

cells with cytoplasmic vacuoles

b-Most warts are **benign** & don't
progress to malignancy



Human papilloma virus (HPV)



B-Effects

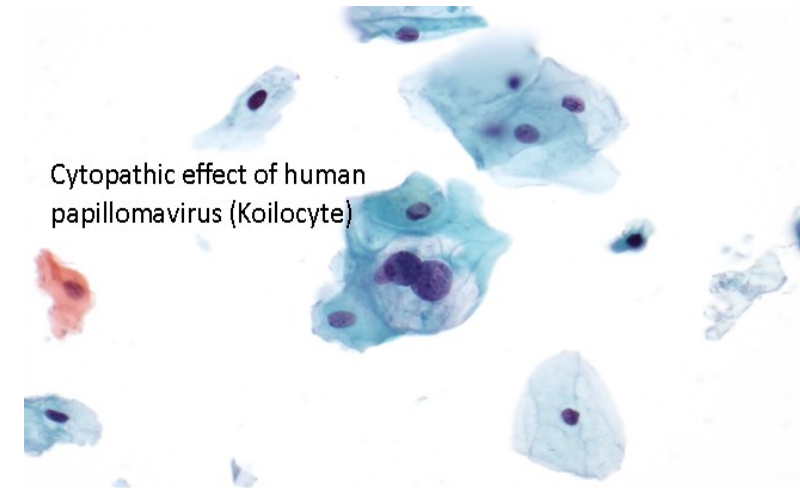
2-Cutaneous HPVs ; All are benign

a-Virus infects **basal cells** of skin **No** virus production

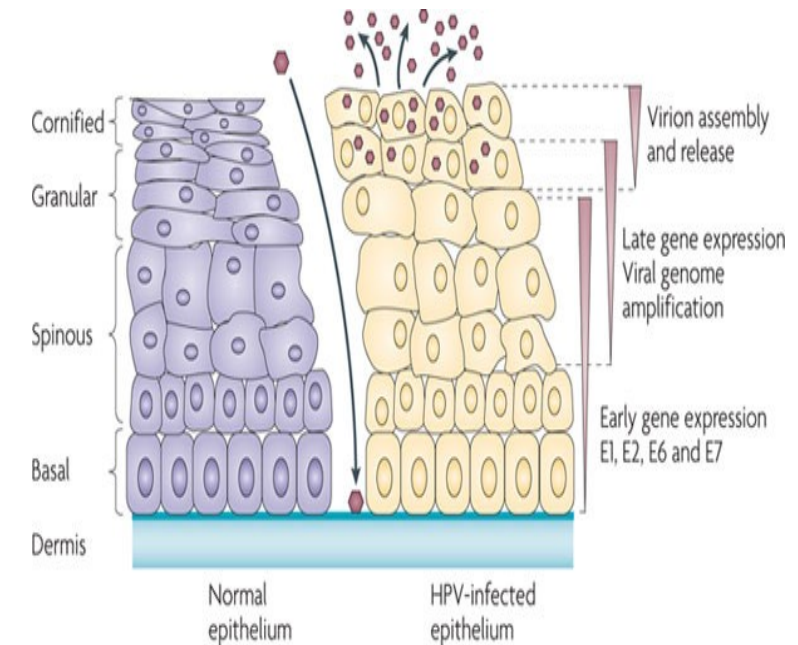
b-Viruses are **produced by squamous cells on the surface**

Efficient transmission

c- There is **hypertrophy of all layers of epidermis & hyperkeratosis**



Cytopathic effect of human papillomavirus (Koilocyte)



Human papilloma virus (HPV)



3- Genital HPVs

a-Most are benign

b- Some, mainly HPV 16 &18,are oncogenic :

associated with carcinoma of cervix , penis & anus

Mechanism of HPV carcinogenesis:

Viral DNA is integrated into host cell DNA **adjacent to cellular protooncogene**

Overexpression of **viral proteins (E6&E7)**

Inactivation of **tumor suppressor proteins p53&RB**

Malignant transformation

Human papilloma virus (HPV)



C-Immunity

Both humoral & cell-mediated immunity

are induced by viral infection

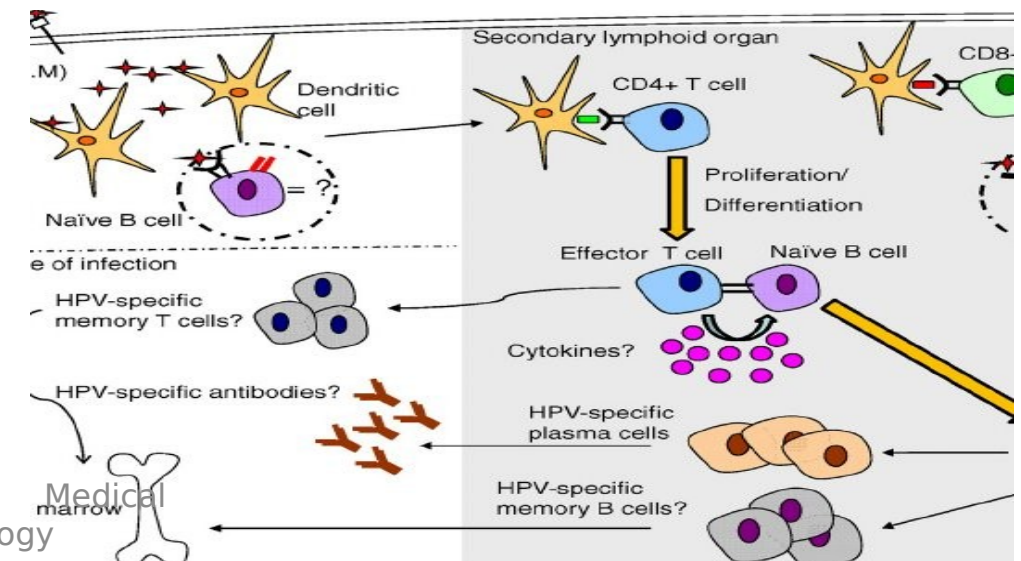
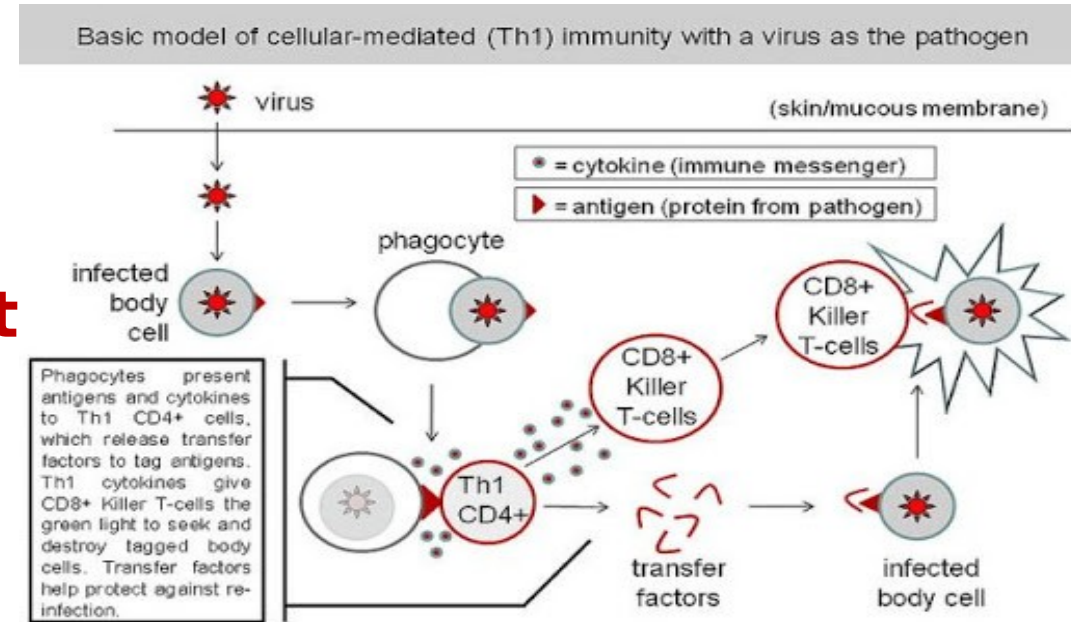
1-Th1&T cytotoxic cells induce

regression of warts

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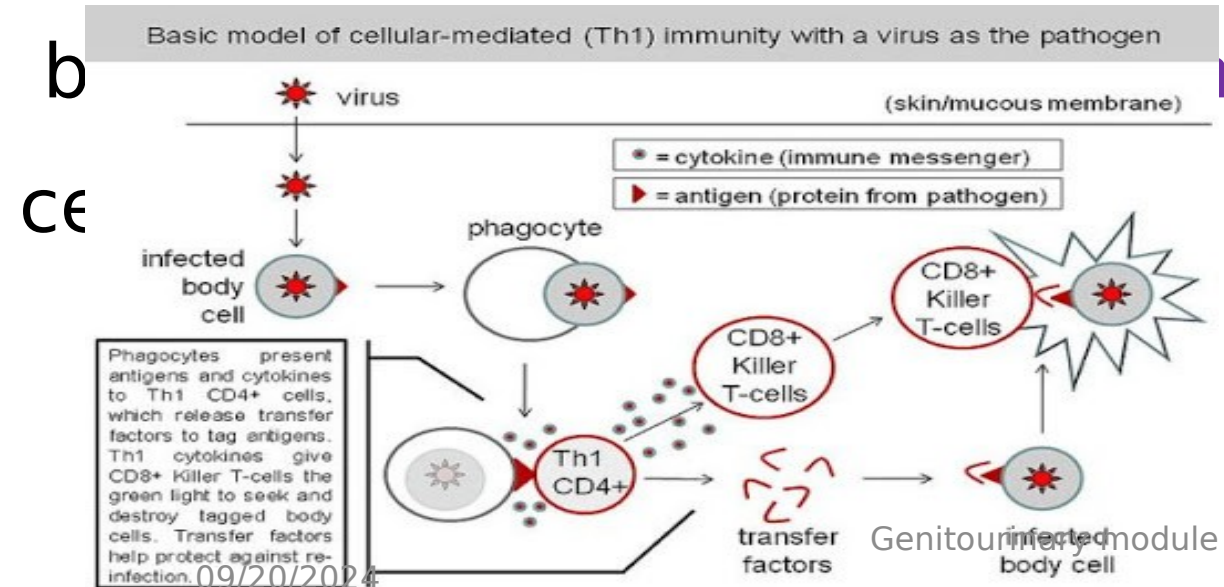
Human papilloma virus (HPV)



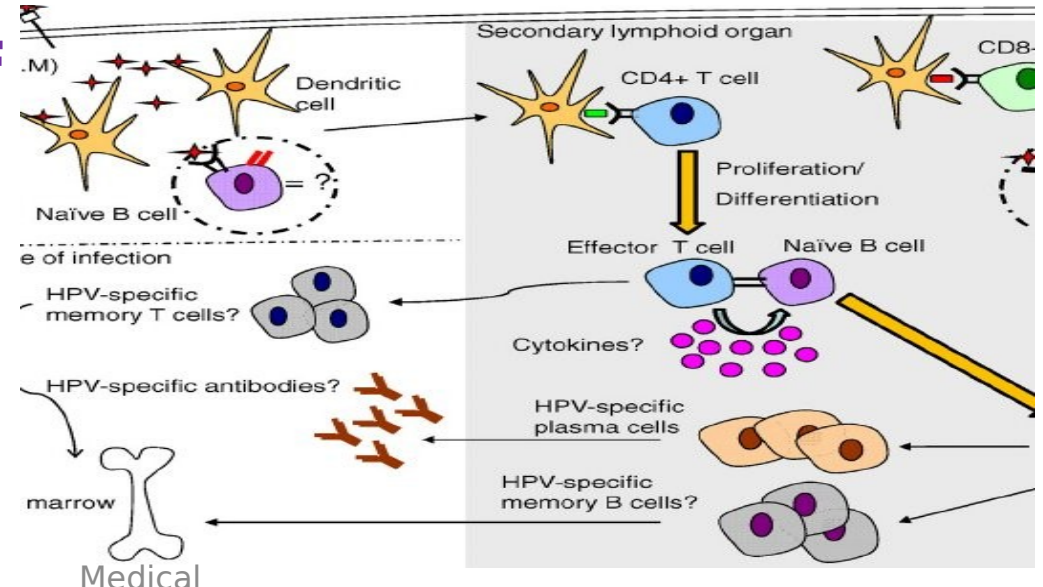
C-Immunity

3-Immunosuppressed patients (e.g patients with AIDS]

a-Have more **extensive** ,persistent or recurrent warts,



ite of



Human papilloma virus (HPV)



Clinical manifestations

A-Cutaneous warts : Self limited (non oncogenic)

Mainly in children & adolescents

1-Common warts (HPV 2 & 4)

On hands & fingers



2-Plantar warts (HPV 1&4)

- On soles
- More deep & painful



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Human papilloma virus (HPV)



Clinical manifestations

B-Oral and laryngeal lesions : Benign & recurrent

1-Laryngeal papilloma (HPV 6&11) :

a- Juvenile : affects children < 5 years :

- From mother **birth canal** infected with genital warts
- If grow → upper airway obstruction (life-threatening)

b-Adults : From **orogenital contact** with infected sexual partner



2-Oral papillomatosis : On oral mucosa & tongue

If multiple → oral **florid papillomatosis**



Human papilloma virus (HPV)



C- Anogenital lesions

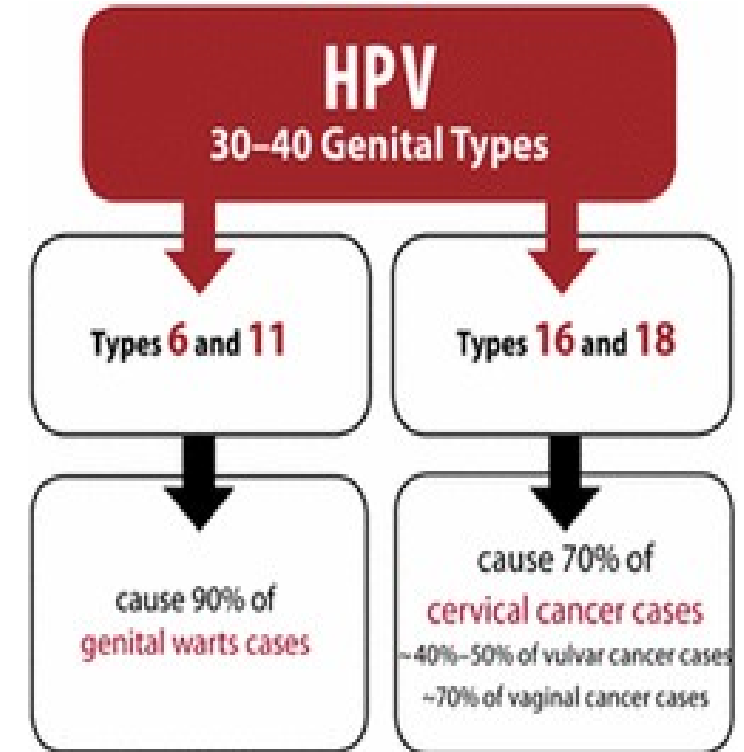
1-Anogenital warts : condylomata acuminata ; mainly by HPV6 &11)

a-Site : ♀ vulva ,vagina ,cervix ♂ : penis & anus

b- Characters :

■ **Painful** or itchy & rarely bleed

■ **Benign**



Human papilloma virus (HPV)



2-Cancer : Mainly by HPV-16 &18.

Premalignant lesions called intraepithelial neoplasia

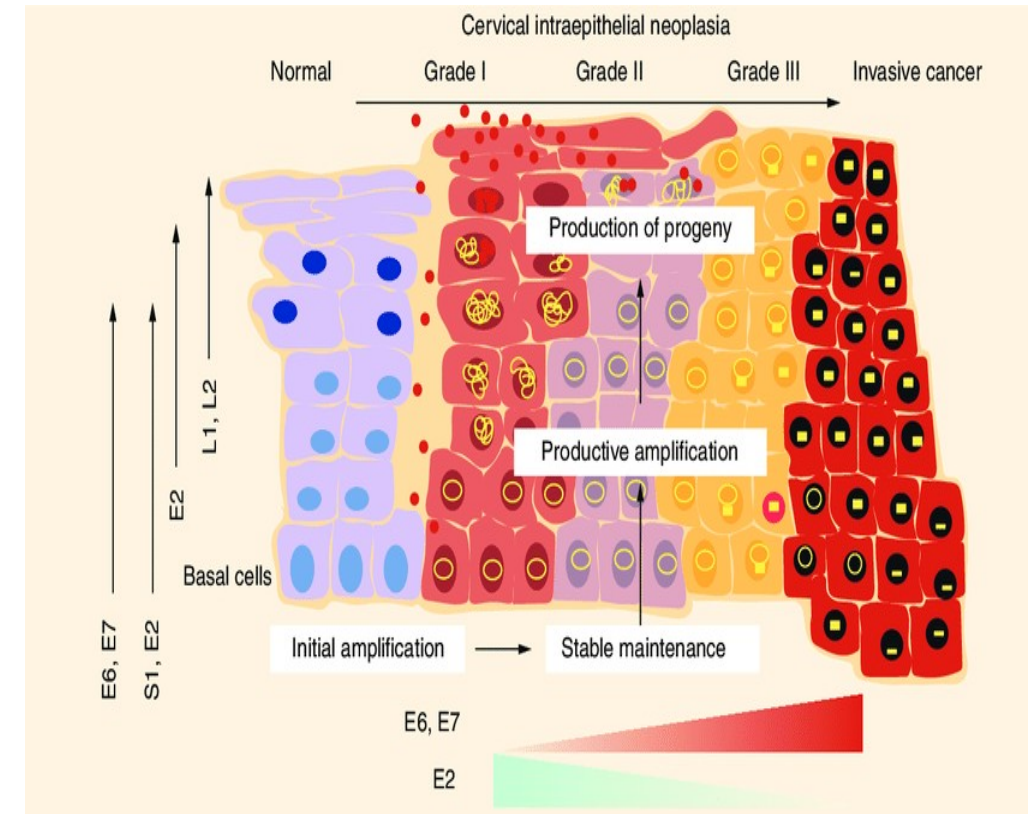
in cervix, penis, and anus



Invasive carcinoma if not treated

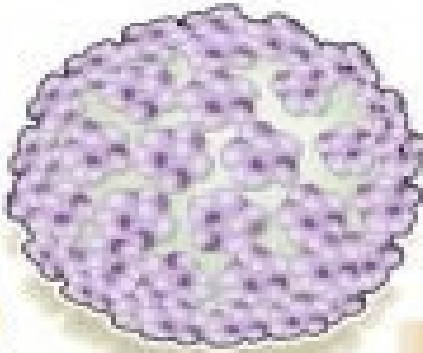
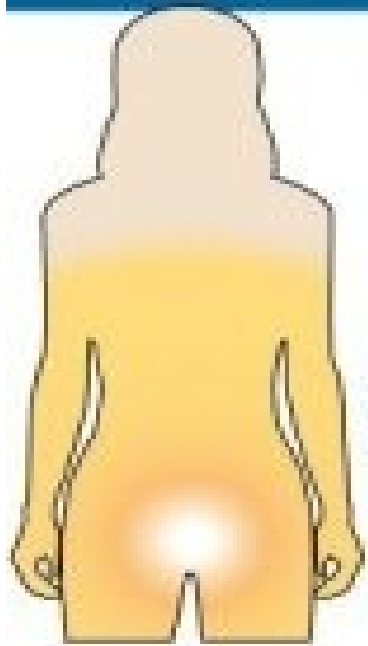
⊙ **Risk factors for malignant transformation**

- Smoking
- Immune status
- Genetic background



Human papilloma virus (HPV)

Sexually transmitted HPV infections are common and often asymptomatic, untreated cases in women are the main cause of cervical cancer



▶ A sexually transmitted virus that causes cancer

▶ More than 100 types of HPV have been found so far

▶ 15 have been identified as putting women at high risk for cervical cancer

Cervical cancer

Virus in cervix enters cells through micro-abrasions



Infected cells



HPV replicates

90 percent of cases heal within two years

Several weeks later

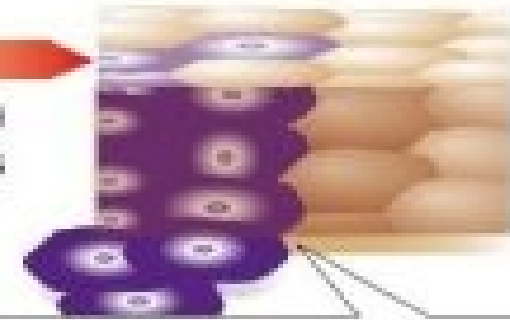


Infection spreads

3

0.8 percent of cases develop cancer

10-30 years later



HPV invades deeper layer of tissues and turns cancerous

Human papilloma virus (HPV)



Laboratory diagnosis (usually diagnosed clinically)

A-Detection of koilocytes in lesions (in cervix by Pap smear)

Infected squamous epithelial cells with **cytoplasmic vacuole**

Limitations

- 1-Not always present
- 2-Not sufficiently specific
- 3-Doesn't differentiate between low & high risk types

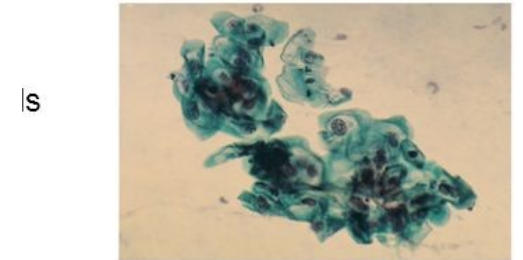
B-PCR or in-situ hybridization : Diagnosis of high risk types

Detection of viral **DNA or RNA transcripts of E6 & E7 oncogene**

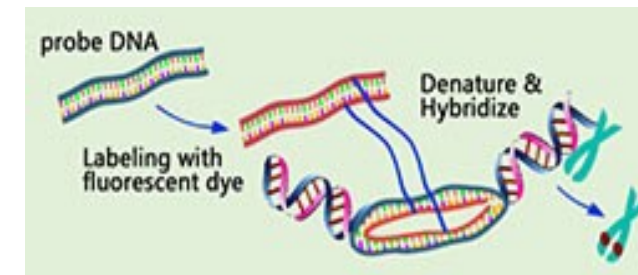
C-Serology : Not useful due to

- 1-No cell lysis or viremia
- 2- Little inflammation & Ab production following natural infection

Koilocytic cells



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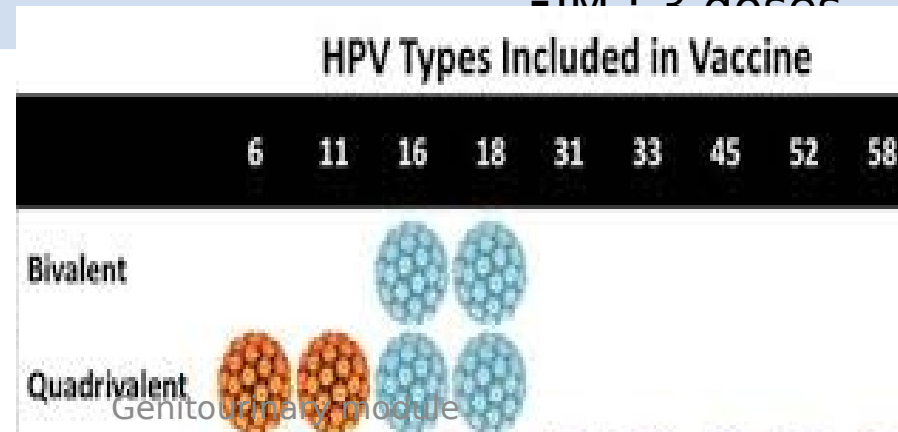
Human papilloma virus (HPV)

Prevention : 2 recombinant vaccines

Types	1 - Gardasil contains capsid proteins of 4 types 6,11 (genital warts)& 16,18 (cancer cervix, penis & anus)	2 - Cervarix contains capsid proteins of 2 types 16,18 + adjuvant called AS04 Enhances Ab production
Indications ■ HPV immunizations have no effect on existing papillomas	Girls & women(11-26 yrs) IM + 3 doses	



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Quiz



Regarding human papillomavirus (HPV), which one of the following statements is most accurate?

- (A) There is no vaccine available against HPV.**
- (B) Acyclovir is effective in preventing lesions caused by HPV**
- (C) HPV encodes proteins that play an important role in malignant transformation .**
- (D) The diagnosis of HPV infection is usually made by detecting cytoplasmic inclusions within giant cells in the lesions.**

D

Human papilloma virus (HPV)



Treatment

1- Podophyllin

the usual treatment for **genital warts**

2-Alpha interferon

better at preventing **recurrences**.

3-Cidofovir

treatment of **severe** HPV infection.

Molluscum Contagiosum Virus (MCV)



Structure

▪

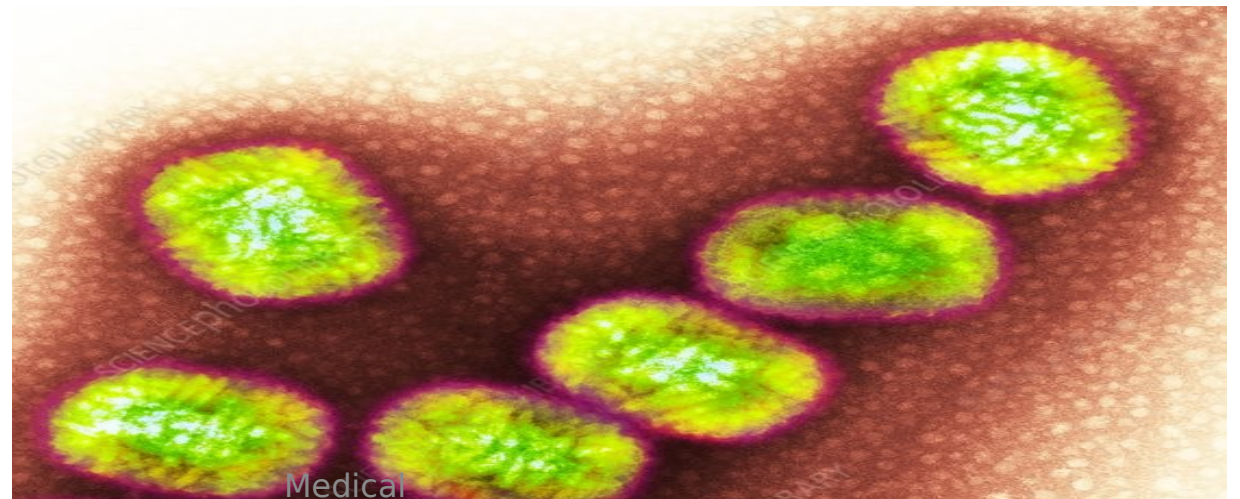
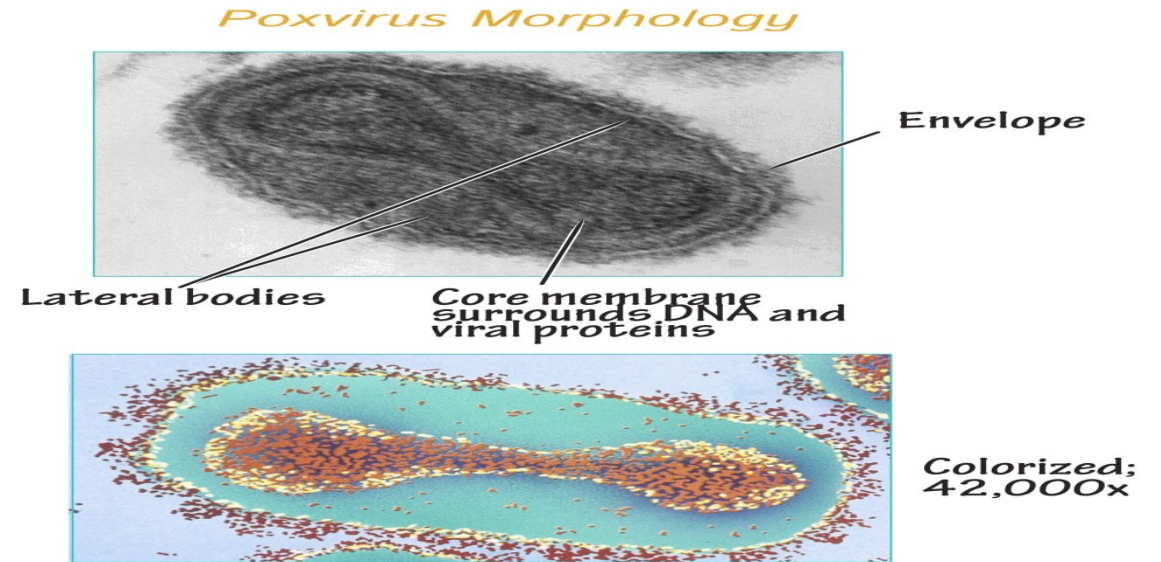
A - Family : Poxviruses

B - Nucleocapsid

1- DNA

2- **Brick- shaped (complex)**

C - Enveloped



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Molluscum Contagiosum Virus (MCV)



Pathogenesis

A – Mode of transmission

1-**Cutaneous** lesions : **close** contact (enveloped)

Direct or indirect (e.g fomites towels)

2.**Genital** lesions : **sexual** contact

B- Effect : Non oncogenic virus

Epithelial proliferation of epidermis extending into dermis

Infected cells show **cytoplasmic eosinophilic inclusion bodies**

Some of inclusions **burst open** when lesion is crushed

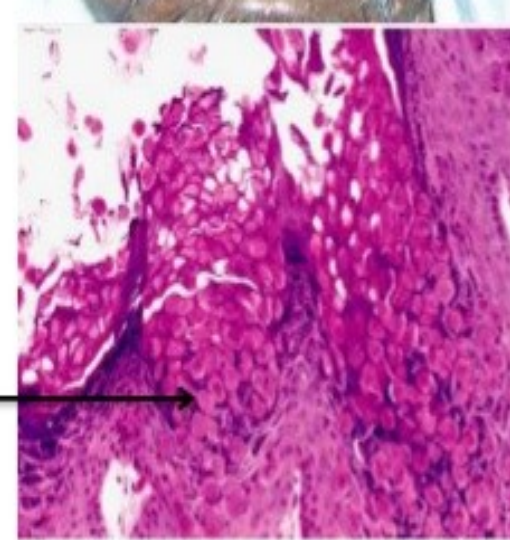
Release large number of viruses

central core.

In AIDS, hundreds of lesions of molluscum contagiosum may be observed, showing little tendency toward involution.

M/E:

Many epidermal cells contain large, intracytoplasmic inclusion bodies, **Molluscum bodies. (H&E 40X)**



Molluscum Contagiosum



Umbilicated



Central keratin plug



Poxvirus

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Molluscum Contagiosum Virus (MCV)



Clinical manifestations :Wart-like lesions

A-Characters

- Small , **umbilicated** with **white core**
- Painless, nonpruritic, and **not inflamed**

B-Site

on the **skin (face)** or
mucous membrane (genitalia & perirectal area)

C-Fate

Self limited → heals spontaneously
(may last few months)

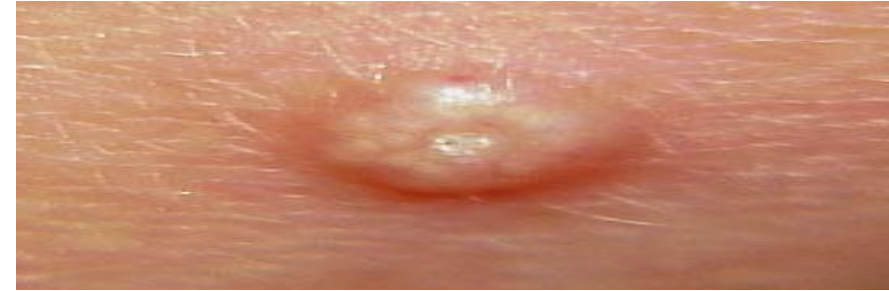
Laboratory diagnosis

1- PCR : detects viral DNA

2-EM : detects viral particle

NB. The virus is a **weak** Ag →

No serological tests





Genital Herpes

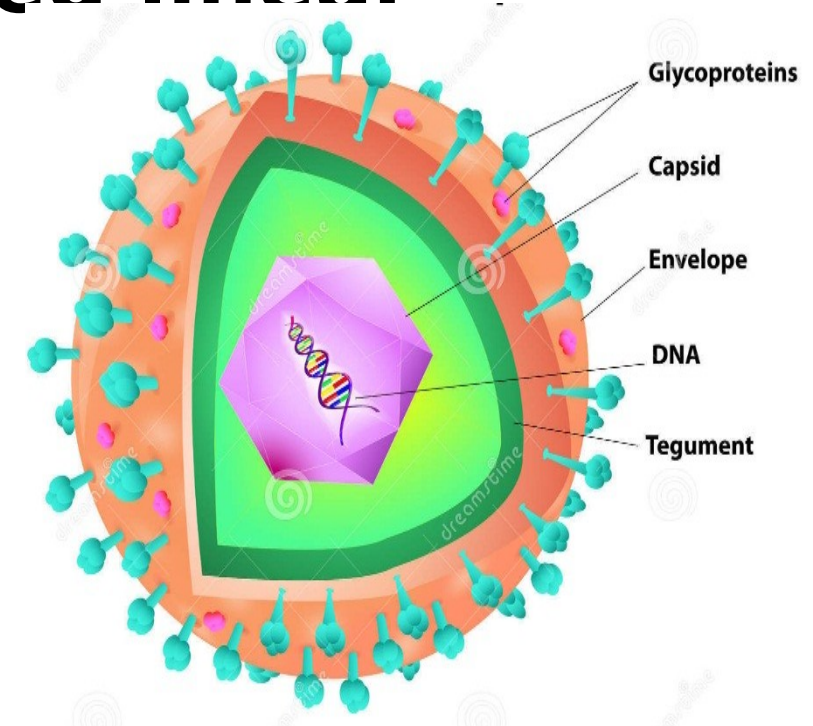


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Herpes Simplex Virus (HSV)



- ✓ **Enveloped virus with an icosahedral nucleocapsid and double-stranded linear DNA.**
- ✓ **Herpes simplex virus type 2, causing infections primarily of the genitals, can remain latent in the lumbar and sacral ganglia.**



Herpes simplex virus type 2 (HSV-2)



Clinical manifestations

A-Herpes genitalis

⊛ Transmitted by sexual contact.

⊛ **Painful vesicles** & ulcers of ♀ & ♂ genitals and area



+ inguinal lymphadenopathy

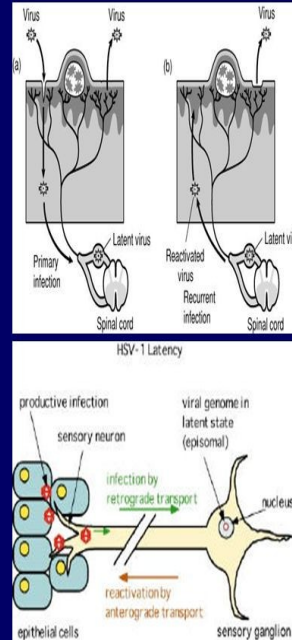


The virus became latent in sacral ganglia

Pathogenesis of HSV-2

Genital herpes infection

- **Primary infection** occurs when HSV-2 infects epithelial cells covering the mucosa.
- The virus then migrates to the nearest ganglion (sacral ganglia) via neurons where it replicates and establish latency for life.
- Once its reactivated, it travels back through neurons to the site of the primary infection and causes **recurrent infection**.
- * Once the virus enters the human body it remains for life (**latency**)



Recurrences Genitourinary module

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Herpes simplex virus type 2 (HSV-2)



Clinical manifestations

- ⊙ **1st infections** are **more severe** than recurrences
- ⊙ **Asymptomatic inf. is common in ♂ (urethra or prostate)**
↓
& ♀ (cervix)

Source of infection to other individuals__

B-Neonatal herpes (see perinatal infections)

Herpes simplex viruses type 2 (HSV-2)

Laboratory diagnosis

1-Direct virus detection in vesicles

a.L/M : **Tzanck smear** (Cells from vesicles stained with Giemsa) **for rapid diagnosis**

- i. Multinucleated giant cells
- ii. Intranuclear inclusion (Cowdry) bodies

b-Fluorescent Ab staining : detects viral Ag

Type-specific monoclonal Abs **distinguishes between HSV1&2**

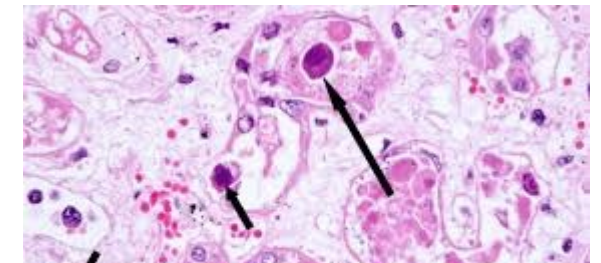
2 .Viral Isolation on tissue culture

Cytopathic effect (CPE): Multinucleated giant cells

3- Serology : Ab detection

In 1ry infection but not in recurrence

(recurrences rarely cause ↑ Ab titer)



Virus Antigen Detection

Direct Fluorescent antibody (DFA) stain

- Collect cells from base of fresh vesicular lesion
- Stain with DFA specific for HSV and/or VZV
- Look for fluorescent cells (virus infected) using fluorescence microscope
- More sensitive & specific method than Tzanck prep (DFA 80% vs. Tzanck 50%)

Tzanck prep= Giemsa stained cells from lesion -/examine for multinucleated giant cells of Herpes

The image shows two side-by-side micrographs. The left one is a Tzanck smear (Giemsa stain) showing multinucleated giant cells. The right one is a DFA stain showing fluorescent cells, indicating viral antigen detection.

Herpes simplex viruses type 2 (HSV-2)



Prevention

1-Avoid contact with skin vesicles

2 -Chemoprophylaxis : Valcyclovir

Effect : Suppresses recurrent lesions & ↓ shedding

Indications :

- a- Patients with frequent recurrences of HSV-2
- b- Immunocompromized individuals e.g transplant r



NB Antiviral drugs don't affect the virus in the latent stage



Quiz

Seeing multinucleated giant cells in a Tzanck smear can be used to make a presumptive diagnosis of infection by which one of the following viruses?

- (A) Epstein-Barr virus**
- (B) Herpes simplex virus 2**
- (C) Human papillomavirus**
- (D) Parvovirus B19**
- (E) Rubella virus**

B



Quiz

• **Which of the following cell types are specific to a latent genital infection with HSV-2?**

- A. Trigeminal ganglia
- B. Sacral ganglia
- C. Vagal nerve ganglia
- D. Neural sensory ganglia

B



Human Herpes Virus type-8 (HHV-8)

Pathogenesis

A- Modes of transmission

1-Sexual 2- Saliva

B- Effect : oncogenic virus

1-On vascular endothelial cells

HHV8 encodes a protein called

latency associated nuclear Ag (LANA)



Inactivation of tumor suppressor genes : RB & P53



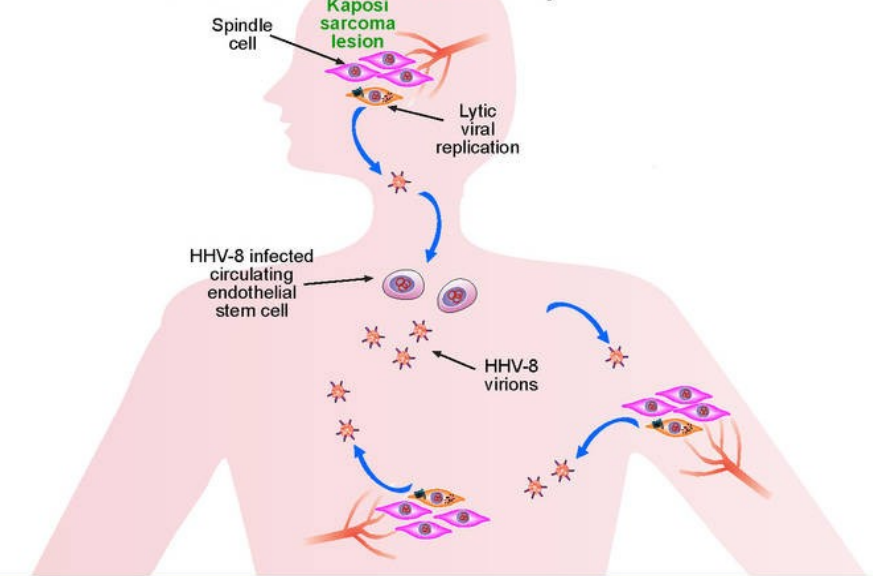
Malignant transformation

2-On B cells

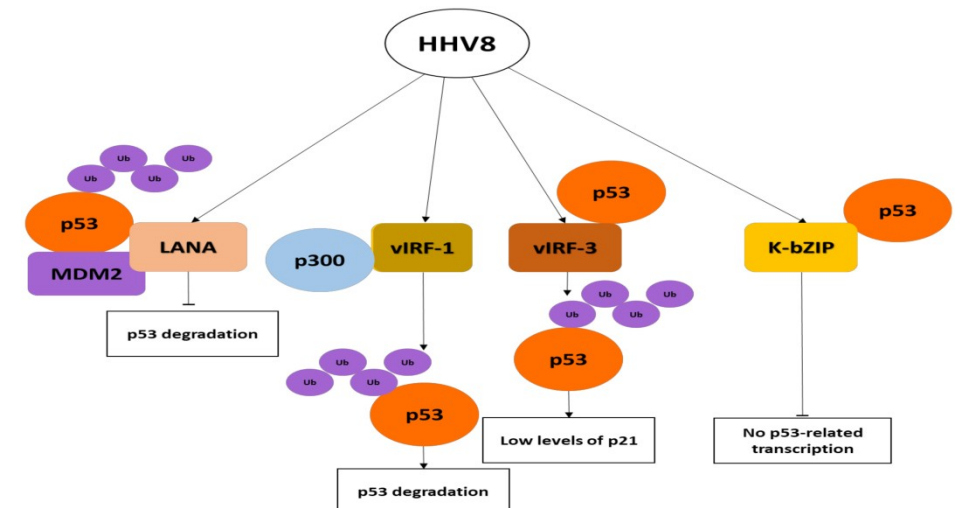
Induces proliferation

Lymphoma

HHV-8 dissemination and development of lesions



Kaposi sarcoma lesions develop in the skin at late stages of HHV-8 reactivation following a failing of the immune system to control virus replication. Dissemination of virus produced by increased lytic replication promotes the development of additional lesions which may also be due to increased infection of circulating endothelial stem cells. Malignancies can also develop at mucosal sites or in other organs. Spindle cells do not appear to metastasise to other sites, rather new lesions develop following free virus infections of endothelial cells or recruitment of infected endothelial cells to the vasculature.



Human Herpes Virus-8



Clinical manifestations

Two malignancies in AIDS patients

1- Kaposi sarcoma :

Purple nodules in skin , oral cavity, GIT & lung

(HHV-8 is also called **Kaposi's sarcoma associated herpesvirus**)

2- Body cavity-based lymphomas Or primary effusion lymphoma

Malignant effusion in pericardial, pleural

or peritoneal cavity

Laboratory diagnosis

PCR : detects viral DNA in skin biopsy

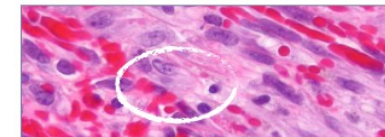
Prevention : **Gancyclovir** & **foscarnet** ↓ Kaposi sarcoma lesion



Kaposi Sarcoma-Related Virus (aka, HHV-8)

- ✓ Kaposi Sarcoma, Primary effusion lymphoma, Castleman's disease
- ✓ Opportunistic AIDS infections
- ✓ Viral genes promote growth of infected cells

Kaposi Sarcoma: tumors develop on skin/mucosal surfaces.



Spindle cells & branching vessels



Anti-viral drugs may prevent Kaposi Sarcoma

Suggested textbooks



- ***Review of Medical Microbiology and Immunology,***
Warren Levinson
- ***pages 491***
639-647
673-677

Thank You